

**Treatment of COVID-19 exacerbated asthma: should systemic corticosteroids be used?**

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**Abstract**

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 infection is a new rapidly spreading infectious disease. Current guidance from the World Health Organisation (WHO) highlights asthmatics as a high-risk group for severe illness from COVID-19. Viruses are common triggers of asthma exacerbations and the current SARS-CoV-2 pandemic raises several questions regarding the optimum management strategies. Here, we discuss the contentious issue of whether the mainstay therapies systemic corticosteroids should be used in the routine management of COVID-19-associated asthma exacerbations. Recent guidance from the WHO has advised against the use of corticosteroids if COVID-19 is suspected due to concerns that these agents may impair protective innate anti-viral immune responses. This may not be appropriate in the unique case of asthma exacerbation, a syndrome associated with augmented type 2 inflammation, a disease feature that is known to directly inhibit anti-viral immunity. Corticosteroids, through their suppressive effects on type 2 inflammation, are thus likely to restore impaired anti-viral immunity in asthma and, in contrast to non-asthmatic subjects, have beneficial clinical effects in the context of SARS-CoV-2 infection.

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86 **Introduction**

87 Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 infection is a new rapidly  
88 spreading infectious disease. Current guidance from the World Health Organisation (WHO)  
89 highlights asthmatics as a high-risk group for severe illness from COVID-19 (2) and  
90 widespread shielding of these patients has been advocated. Published case series of COVID-  
91 19 have not reported asthma as a common comorbidity (22) and there is currently limited  
92 evidence to inform on the optimum management of COVID-19 associated asthma  
93 exacerbations. Here, we discuss the contentious issue of whether the mainstay therapies  
94 systemic corticosteroids should be used in the routine management of COVID-19-associated  
95 asthma exacerbations.

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97 **Viruses and SARS-CoV-2 as triggers for asthma exacerbations**

98 Asthma is a chronic respiratory condition, punctuated by the occurrence of acute  
99 symptomatic deteriorations ('exacerbations'). The link between virus infection and  
100 exacerbations is well established: rhinoviruses are the most commonly isolated pathogen at  
101 exacerbation (~50-80% of virally triggered episodes) with a range of other viruses (including  
102 coronaviruses) less frequently identified (17, 23). Experimental human infection challenge  
103 studies have confirmed unequivocally that viruses play a causal role in precipitating asthma  
104 exacerbations (10), driving augmented airway inflammation, mucus hypersecretion and  
105 lower respiratory tract symptoms (8, 10, 12). As with other coronaviruses, SARS-CoV-2 is  
106 anticipated to similarly exacerbate disease, although the precise immunopathological  
107 mechanisms through which this occurs are yet to be characterised.

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109 **Systemic corticosteroids in asthmatics with COVID-19: beneficial or harmful?**

110 Current asthma guidelines advocate treatment with oral corticosteroids in acute  
111 exacerbations (typically oral prednisolone 40 - 50mg for 5 to 7 days (1)) and this therapy is  
112 prescribed almost ubiquitously for hospitalised episodes. Asthma exacerbations are  
113 associated with augmented airway inflammation which drives increased respiratory  
114 symptoms (10); corticosteroids are broad immunosuppressive agents that reduce these  
115 features to promote clinical recovery. Conversely, recent guidance from the WHO advises  
116 against the use of corticosteroids if COVID-19 is suspected, although with a caveat that they  
117 may be considered if there is underlying asthma or COPD (2). The recommendation of  
118 avoidance has been formulated based on previous data showing that, despite potentially  
119 beneficial anti-inflammatory effects, corticosteroids (inhaled or systemic) can inhibit  
120 production of the critical anti-viral mediators type I and III interferons. This has been shown  
121 in a range of *in vitro* and *in vivo* human and animal studies for several asthma-relevant  
122 viruses including rhinovirus, influenza and respiratory syncytial virus (RSV) (7, 18, 19). These  
123 effects precipitate increased virus replication (7, 18, 19) and augment virus-driven  
124 pathology including mucus hypersecretion and secondary bacterial infections (18). Similar  
125 detrimental effects are expected to occur with use of corticosteroids in the context of

COVID-19. Accordingly, studies in patients with other coronavirus infections (e.g. SARS-CoV1, MERS-CoV) have shown that corticosteroids increase viraemia and delay viral clearance with no evidence of clinical benefit (16).

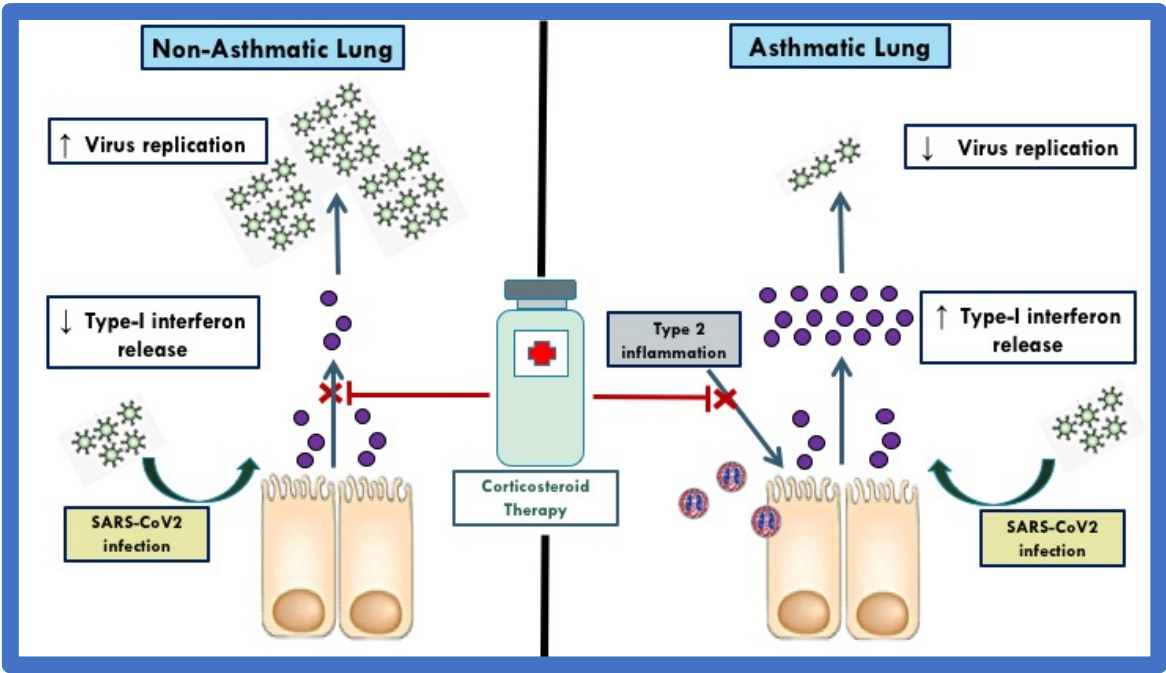
Asthma is associated with an inherent impairment of interferon responses to virus infection (4, 20) and, therefore, in the context of overwhelming viral illness, further inhibition of interferon by corticosteroids in an already deficient state could have deleterious consequences. This leaves clinicians with the conundrum of whether oral corticosteroids, which are effective guideline-recommended therapies for asthma exacerbations, should be used in COVID-19-related exacerbation. However, multiple other lines of evidence in asthma indicate that certain disease mechanisms might counterbalance any potential adverse effects upon anti-viral immunity. Increased T-helper cell 2 (Th2) inflammation is present in a large proportion of asthmatic subjects and is augmented upon viral infection (10, 12). Sputum eosinophilia correlates negatively with impaired IFN induction in cultured asthmatic cells (4) and Th2 mediators (IL-4, IL-13) can directly inhibit epithelial production of type-I interferon (3). Interferon- $\alpha$  can additionally suppress Th2 cell polarization in T cell or mixed leukocyte culture models, attenuating expression of GATA3, IL-4, IL-5 and IL-13 (9, 14). Furthermore, mice deficient in the type I IFN receptor-deficient mice (*Ifnar*<sup>-/-</sup>) have augmented pulmonary eosinophilia and type 2 inflammation in response to influenza infection (5). As corticosteroids suppress type 2 inflammation, their use in the context of COVID-19 associated exacerbation may thus lead to the beneficial effect of secondary restoration of impaired anti-viral immunity (see **Figure 1**). This was suggested by a previous study showing that inhaled budesonide did not impair CD8<sup>+</sup> T cell infiltration into the bronchial epithelium following experimental rhinovirus infection in asthmatics (6) contrary to the clear suppressive effects of corticosteroids on T cells observed in the absence of pre-existing Th2 inflammation (18). Accordingly, in a recent report of histopathological autopsy findings from a non-asthmatic patient with COVID-19 treated with systemic corticosteroids, suppressed peripheral blood CD8<sup>+</sup> T cell numbers were observed (21).

In a clinical setting, objective evidence of augmented type 2 inflammation could be ascertained by the presence of bronchoconstriction (since type 2 mediators, particularly IL-13, are major drivers of airway hyperresponsiveness) or by measurement of objective biomarkers of type 2 inflammation such as blood eosinophils. Interestingly, in case series to date, SARS-CoV2 infection appears to be associated with low blood eosinophils (15). A future hypothesis to explore is whether the presence of normal or elevated eosinophils in asthmatics infected with SARS-CoV-2 may reflect a type 2 inflammatory process that could be used as a biomarker for corticosteroid therapy. Although systemic steroids are highly effective in eosinophilic disease, exacerbations of airways disease are heterogeneous and viral exacerbations may also be characterised by neutrophilic inflammation (11) which is typically less responsive to steroids. It is currently unclear whether steroids can be safely withheld in patients with low blood eosinophil counts, although studies addressing this

question are needed. Moreover, early data suggests that the primary focus of lung pathology in COVID-19 may be the parenchyma rather than the airways with evidence of diffuse alveolar damage, pneumocyte desquamation and interstitial mononuclear inflammatory infiltrates reported (21). It remains unclear whether more prominent bronchial involvement will be observed in asthmatic subjects and larger case series with inclusion of such patients should shed light on this.

**Concluding remarks and Future Perspectives**

We remain in the early stages of our understanding of how COVID-19 affects patients with chronic respiratory diseases such as asthma and optimum management strategies still need to be determined and refined. However, the contraindication to corticosteroids that is being advocated for individuals who acquire SARS-CoV2 infection, is predominantly based on a lack of efficacy in treating COVID-19 disease, rather than evidence of harm. This should be balanced against their proven efficacy in reducing asthma symptoms and risk of relapse in patients with asthma (13), particularly those with evidence of augmented type 2 inflammation where corticosteroid use may restore anti-viral immunity and confer benefit. The decision to treat an asthmatic infected with SARS-CoV-2 will therefore require careful consideration on a ‘per-patient’ basis. Future studies should focus on characterising the immunopathology of COVID-19-related asthma exacerbation including the extent to which augmented type 2 inflammation drives pathology. This will facilitate determination of the optimum approaches to management of these patients.



**Figure 1:** Proposed differences between effects of corticosteroid therapy in asthmatic and non-asthmatic subjects infected with SARS-CoV2.

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